Design and Validation of a Particle Size Characterization Method for Sacubitril/Valsartan API

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ABSTRACT

Sacubitril, a neprilysin inhibitor, is widely used in combination with Valsartan as part of the Angiotensin Receptor Neprilysin Inhibitor (ARNI) therapy for managing heart failure with reduced ejection fraction. Despite extensive research on its pharmacological and analytical profiles, the literature survey indicated the absence of an established method for determining the particle size distribution of Sacubitril/Valsartan active pharmaceutical ingredient (API). Since particle size plays a critical role in influencing the dissolution behavior, bioavailability, and overall performance of the final dosage form, the development of a reliable analytical technique is essential. In the present study, a laser diffraction-based method was developed using the Malvern Mastersizer system to measure particle size distribution for Sacubitril/Valsartan API. Appropriate dispersant selection, optimized instrumental parameters, and standardized sample preparation procedures were implemented to achieve consistent dispersion and accurate readings. Key parameters such as obscuration range, refractive index, stirring speed, and measurement cycles were optimized to obtain reproducible results. The method was further subjected to analytical validation, including precision, intermediate precision, and robustness. The results demonstrated acceptable percentage RSD values across d(0.1), d(0.5), and d(0.9), confirming the method's precision and ruggedness. All validation parameters met the predefined acceptance criteria, indicating that the developed laser diffraction technique is suitable for routine quality control analysis of Sacubitril/Valsartan API. Thus, this study successfully establishes a scientifically sound and validated particle size distribution method that can support the manufacturing and quality assurance of ARNI-based formulations.

Keywords: Sacubitril/Valsartan; Particle Size Distribution; Laser Diffraction; Method Development; Validation

INTRODUCTION

Sacubitril is a first-in-class neprilysin inhibitor used primarily as part of the combination drug Sacubitril/Valsartan (Angiotensin Receptor Neprilysin Inhibitor, ARNI) for the treatment of heart failure with reduced ejection fraction (HFrEF). Developed to overcome the limitations of conventional therapies such as ACE inhibitors and ARBs, Sacubitril enhances the body's endogenous natriuretic peptide system, providing improved cardiovascular outcomes. The combination therapy has demonstrated superior efficacy in reducing mortality and hospitalization in heart failure patients, making it a major advancement in modern cardiovascular pharmacotherapy.[1] Sacubitril is administered as a prodrug, sacubitril sodium, and is rapidly converted to its active metabolite LBQ657. This active form inhibits neprilysin, a neutral endopeptidase responsible for degrading vasoactive peptides such as natriuretic peptides (ANP, BNP), bradykinin, and adrenomedullin. By blocking neprilysin, LBQ657 increases circulating levels of these peptides, promoting vasodilation, natriuresis, diuresis, and reduced sympathetic drive.[2] This leads to decreased preload and afterload, improved cardiac output, and attenuation of cardiac remodeling. Since neprilysin inhibition alone can increase angiotensin II levels, Sacubitril is combined with Valsartan to simultaneously block the renin–angiotensin–aldosterone system (RAAS), ensuring balanced hemodynamic effects. Sacubitril is a white to off-white crystalline powder with a molecular formula $C_{24}H_{29}N_3O_5$ and a molecular weight of approximately 435.50 g/mol.[3] The active prodrug form, sacubitril sodium, is slightly soluble in water and exhibits moderate lipophilicity. It has a pKa around 4.8, supporting partial ionization under physiological pH conditions. Sacubitril decomposes upon prolonged exposure to moisture and should be stored in a dry, controlled environment. Its chemical structure contains a substituted biphenyl moiety and an ethyl ester functionality, which is responsible for its conversion to the active carboxylate metabolite.[4] The literature review indicated that, despite multiple related studies [5-15]. No specific method has been reported for assessing the particle size distribution of Sacubitril/Valsartan API. Consequently, research was carried out to formulate a suitable particle size analysis procedure for this API, and additional studies were performed to validate the developed method.

MATERIALS AND METHODS

Drugs and chemicals

Sacubitril Valsartan API, Silicone oil

Instrumentation

The Malvern master sizer 3000, Hydro 3V. Mastersizer Software (Version 3.88) was used for data processing and evaluation.

Instrumental parameters

Malvern Mastersizer 3000, equipped with Wet Dispersion Unit (Hydro MV). The dispersant identified as Silicone oil. The Dispersant RI and Sample RI were 1.4694,1.590 respectively. Following instrument parameters were Sample absorption - 0.1, Sample measurement time - 6 seconds, and. Background Measurement time - 6 seconds, Range of obscuration range was 5-10%, Configured stirrer speed 2000 rpm and number of measurement cycle 3. The acquired

outcomes of d(0.1), d(0.5), and d(0.9) readings of analysis and obscuration was achieved satisfactory.

Sample Preparation

Accurately weigh and transfer about 200-mg of sample into a 50 mL graduated stoppered test tube. Add 5 drops of the dispersant and mix using a glass rod to form a uniform paste. Add 10 mL of the dispersant and vortex for one minute. Sonicate for 1 minute for even dispersion of particles. Transfer the sample to the sampling unit dropwise (for about 1 minute) using transfer pipette until obscuration reaches in between 10%-30%. Wait for about 5 minutes for the obscuration to stabilize.

Procedure

Fill the Sampling Unit to the rim with dispersant solution. From the toolbar select Configure: Accessories. Gradually increase the Stirrer/Pump to 2000 RPM manually. Some dispersant solution in the unit will be displaced, refill the Sampling unit to the rim with dispersant solution. Confirm the instrument settings as per SOP for Malvern Mastersizer 3000, wet analysis mode using the instrumental parameters. Ensure there are no air-bubbles in the Sampling unit (degas three to four times). From the toolbar, select Start SOP and choose the existing SOP. Click Open to start the background measurement. If the laser intensity of the background measurement is <50%, drain the Sampling unit, repeat the cleaning procedure, then proceed from initial stage. Enter sample information and labels for the measurement. Add sample dispersion to Sampling unit using transfer pipette until obscuration attains in between 10% - 30% (oscillating blue bar on green field). Record and print the Average results.

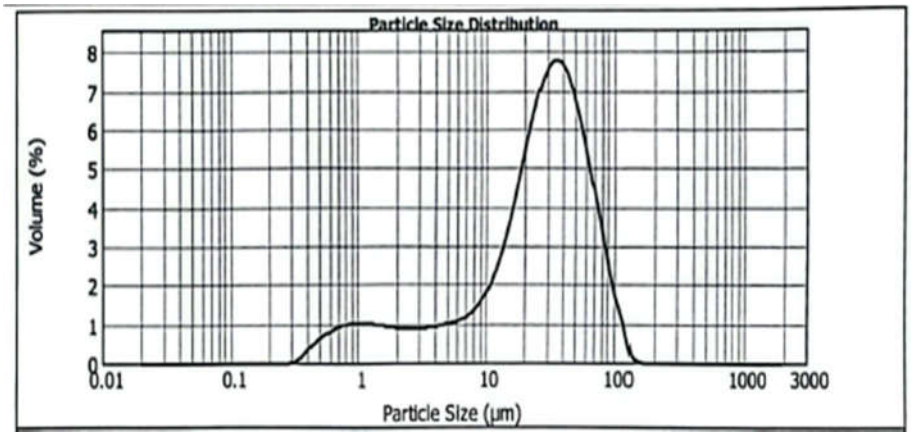

Figure 1: Histogram for Sacubitril/Valsartan PSD

Conclusion

A particle size distribution method for Sacubitril/Valsartan API was developed and validated using the laser diffraction technique. During validation, the method showed good precision, with percentage RSD values of 4.14% for d(0.1), 2.15% for d(0.5), and 2.65% for d(0.9). Intermediate precision results were also within acceptable limits, yielding RSDs of 3.02% for d(0.1), 6.25% for d(0.5), and 4.35% for d(0.9), confirming that the method is rugged. All evaluated parameters met the specified acceptance criteria, demonstrating the method's robustness. The obtained results complied with the acceptance range, with percentage RSD values between 3.25% and 6.25% for d(0.1), 2.32% to 3.13% for d(0.5), and 2.32% to 2.45% for d(0.9). Overall, the compiled analytical data confirmed that the method development and validation were satisfactory. Hence, the established laser diffraction technique is suitable for the particle size analysis of Sacubitril/Valsartan API.

ACKNOWLEDGEMENT

The authors wish to acknowledge the following institution for their support on this research work: Srinivasan College of Pharmaceutical Sciences-Trichy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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